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Introduction: Around 33-46% of Parkinson's disease (PD) patients have REM sleep behavior disorder (RBD), and evidence suggests that REM behavioral events (RBEs) are a prodromal stage of RBD. Few studies have investigated other electrophysiological changes other than REM sleep without atonia in PD patients with RBD. This work has two aims: 1) to develop a data-driven model that, based on sleep electroencephalogram (EEG) and electrooculogram (EOG), can identify RBD in PD patients; and 2) to apply the developed model to PD patients with RBEs to evaluate its ability to predict their progression to full-blown RBD.

Materials and methods: We analyzed video-polysomnography (v-PSG) data in a baseline study of 107 *de novo* PD patients, of whom 54 had normal REM sleep (PDnonRBD), 27 had RBEs (PD+RBE) and 26 had definite RBD (PD+RBD). The patients were re-evaluated with v-PSG at 2-year follow-up (FU).

We included C3-A2, C4-A1 EEG and LOC-A2, ROC-A1 EOG signals in our analysis. We first applied a validated automated macro-sleep (30-s epochs) and micro-sleep (5-s mini-epochs) staging algorithm. Features describing micro-sleep structure, as well as features describing EEG spectral content, EEG complexity, EEG coherence and EOG time-frequency energy were extracted. All the features were given in input to a machine learning system consisting of an ensemble of random forest classifiers, giving as outputs the probabilities of having RBD or not (*P*(RBD) and *P*(nonRBD) respectively). A participant was classified as having RBD if *P*(RBD) exceeded *P*(nonRBD).

The developed system was applied to PDnonRBD and PD+RBD groups to evaluate accuracy, sensitivity and specificity of RBD identification and we identified the features that mainly contributed to a successful RBD detection. Then, it was applied to PD+RBE patients and we evaluated with receiver operating characteristic analysis whether *P*(RBD) could distinguish the 9 participants that developed full-blown RBD at FU from the other 16 ones that did not.

Results: RBD could be detected with accuracy, sensitivity and specificity over 80%. Features describing micro-sleep structure played a major role in correct identification of RBD and we observed that PD+RBD patients were characterized by increased wake-sleep transitions, REM fragmentation and REM instability compared to PDnonRBD. PD+RBE patients that developed RBD at FU study showed significantly higher *P*(RBD) and could be differentiated from the ones that did not (area under the receiver operating curve of 0.87, sensitivity of 77.8% and specificity of 87.5%).

Conclusions: We developed a data-driven model able to identify RBD from EEG and EOG and to predict progression from RBEs to definite RBD in PD patients. The increased micro-sleep instability in PD+RBD might suggest dysfunction of sleep-wake

regulation in PD with RBD and support the hypothesis that PD+RBD patients have more severe neurodegeneration. The results further confirm RBEs as prodromal stage of RBD and, as micro-sleep instability has high importance in identification of RBD, micro-sleep instability might be considered as a biomarker for progression from the prodromal stage of RBD to full-blown RBD in PD patients.